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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,542	10/27/2005	Claudia Bagutti	1-32724A/FMI	4726

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,542	BAGUTTI ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *10,11,14-30 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,13 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1-9, 12, 13, 31-33, teneurin-1, in the reply filed on 01/28/08 is acknowledged.

The traversal is on the following ground(s): The claimed invention encompasses a group of inventions which are linked to form a single, general inventive concept, i.e., detection of teneurin signaling, by a variety of readouts. There needn't be a distinction drawn between methods of detecting teneurin signaling by measuring (i) the cleavage product (e,g., cleaved teneurin-1), or (ii) the biological activity of cellular targets thereof (e.g., PML, zic, ponsin, p53, or myc). Since the teneurin signaling mechanism of action event is the same, it would not be unduly burdened by conducting searches because the search would revolve around the same signaling pathway, irrespective of the number of possible readouts.

This is not found persuasive because the methods of detecting teneurin signaling that measure the biological activity of cellular targets thereof (e.g., PML, zic, ponsin, p53, or myc) do not use the same composition as the method of group I.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group I, claims 1-9, 12-13, 31-33, teneurin-1 protein, are examined in the instant application. The embodiment of claims 1-9, 12-13, 31-33, as drawn to teneurin-2, teneurin-3 and teneurin-4 are withdrawn from consideration as being drawn to non-elected invention. Claims 10-11, 14-30, 36-38 are withdrawn from consideration as being drawn to non-elected invention.

Information Disclosure Statement

The information disclosure statement of 10/27/05 belongs to another application, 10/528439, and therefore the submitted references are not considered.

Objection

1. Claim 3 is objected to for the seemingly typographic error "turnout" cells. This objection could be obviated by amending the claim, for example, by replacing "turnout" with "tumor".

2. Claims 9, 12-13 are objected to for the use of the abbreviated language "GFP" and "YFP" in claim 9.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "said cleaved tenascin" in claim 12 to which claim 13 depends. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 12-13, 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that vertebrate teneurin-1 is a transmembrane protein, and that chicken teneurin-1 is shown to be expressed in specific region of the central nervous system (p.1-2). The specification discloses that however, little is known about the function of the teneurins (p.1-2, especially p.2, third paragraph). The specification discloses that cotransfection of the N-terminal, cytoplasmic domain of teneurin-1, the teneurin-1b (amino acids 156-300), and ponsin, the **cytoplasmic domain** Teneurin-1b binds to and **translocates together with ponsin into the nucleus** (p.32). The specification discloses that antibody to the **N-terminus** of a transfected

teneurin-1 fragment, containing the N- terminal **transmembrane and cytoplasmic domains** of 218 amino acids stains **all membrane**, and in addition **the nuclei** (p.39, p.40, second paragraph).

The specification speculates that thus teneurin-1 and ponsin will influence each other function in the regulation of cell adhesion, cytoskeleton assembly and possibly transcription (p.32, last line, bridging p.33). The specification discloses that ponsin (also known as SH3P12, CAP or FLAF2) gene encodes a protein belonging to the Ponsin/ArgBP2/venexin family, and that all members of this family contain three SH3 domains (p.3, third paragraph). The specification discloses that it is through these SH3 domains that Ponsin protein interacts with Vinculin, an F-actin binding protein, at cell-cell and cell-matrix adherens junctions or with Afadin at Zonula adherens (p.3, third paragraph). The specification discloses that Ponsin also directly interacts with the non-receptor focal adhesion tyrosine kinase p125 FAK (p.3, third paragraph). The specification discloses that several splice variants of Ponsin mRNA exist, which are specifically up-regulated by p53 expression in EB-1 cells and by adriamycin treatment of TK6 cells (p.3, third paragraph).

The specification discloses that it is suggested that teneurin-1 could function as receptor protein, transmitting signals to the cell interior upon homo- or heterophillic binding of a ligand or as a membrane bound ligand (p.2, third paragraph). The specification recites Oohashi et al, 1999, J Cell Biol, 145: 563-577, asserting that mouse Ten m1 is found to exhibit homophilic binding and thereby initiate a signal transduction pathway (p.3, first paragraph). The specification recites Brown et al, 2000, Cell, 1000: 391-398, and discloses that one potential scenario by which transmembrane proteins can fullfill their role as signaling molecules is by regulated intramembrane proteolyis (RIP) (p.2, last paragraph, bridging p.3), i.e. the transmembrane

protein is cleaved first from the extracytosolic segment, which cleavage is a prerequisite for the second cleavage **within** the plane of **the membrane** to liberate the transmembrane domain from the cytosolic fragments, that enter the nucleus (Brown et al, p.391, second column, last paragraph). The specification speculates that proteases, such as site-1 proteases, site 2 proteases, or alpha-, beta-or gamma-secretase, which are known to be involved in RIP, could cleave teneurin-1 at the membrane to separate the intracellular part (cytoplasmic domain) from the transmembrane domain (p.10, first paragraph).

The specification, however, does not have any data or objective evidence that a signal pathway is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei. The specification does not have any data or objective evidence that a signal pathway involved in cell adhesion, cytoskeleton assembly or transcription is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei. The specification does not have any data or objective evidence that downstream proteins, including those from a pathway influencing cell adhesion, cytoskeleton assembly or transcription, are modulated temporally and spatially in response to the translocation of the cleaved, cytoplasmic domain of teneurin-1 and ponsin into the nuclei. Further, a review of Oohashi et al, 1999, cannot find any data or concrete evidence showing a signaling pathway is induced upon homo-dimerization of the mouse Ten m1. A review of Brown et al, 2000, cannot find any data or concrete evidence that teneurin-1 is involved in the RIP processes.

Further, the specification does not have any data or objective evidence that the cytoplasmic domain of teneurin-1 and ponsin are detected in nuclei of normal neurons or tumor cells. In other words, there is no data or objective evidence that in normal neurons or in tumor

cells, the full length teneurin-1 would be cleaved twice, resulting in a free cytoplasmic domain, which is translocated together with ponsin into the nucleus. The specification only has data showing that in C. elegans cells cotransfected with the N-terminal transmembrane and cytoplasmic domains of teneurin-1, and ponsin, the cytoplasmic domain and ponsin are detected in the nuclei. The specification does not have any data or evidence that proteases, such as site-1 proteases, site 2 proteases, or alpha-, beta-or gamma-secretase, which are known to be involved in RIP, have as substrate, teneurin-1, and cleave the full length teneurin-1 twice, first the extracellular domain from the transmembrane and cytoplasmic domains, and then the transmembrane domain from the cytoplasmic domain, to liberate the cytoplasmic domain.

1. Claims 1-9, 12-13 are rejected under 112, first paragraph for lack of enablement for **a method for detecting teneurin-1 signaling**.

One cannot predict that a signal pathway, or a signal pathway involved in cell adhesion, cytoskeleton assembly or transcription is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei, because binding to ponsin and translocation of the cytoplasmic domain of teneurin-1 and ponsin to the nucleus alone is not sufficient to indicate induction of a signal pathway, which involves a cascade of events from downstream proteins. One cannot predict which cascade of proteins, or whether there exist cascade of proteins that are modulated upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei, resulting for example in changes in cell adhesion, cytoskeleton assembly or transcription.

Further, one cannot predict that the cleaved cytoplasmic teneurin-1 is found in the **nuclei of normal neuron or tumor cells** together with ponsin as claimed in claims 3-4, because one

cannot predict whether the homodimerized form of teneurin-1 allow cleavage of the extracellular domain, in view that the mouse ten-m protein may be expressed in a form which does not allow cleavage of the extracellular domain, as taught by Oohashi et al (Oohashi et al, 1999, supra, p.575, first column, last three lines of the paragraph under the title "Structure of the ten-m protein family").

In addition, one cannot predict which **cellular component** to administer into a cell, as claimed in claim 5, which cellular component would cleave full length teneurin-1, because one cannot predict that proteases, such as site-1 proteases, site 2 proteases, or alpha-, beta-or gamma-secretase, which are known to be involved in RIP, also have as substrate, teneurin-1, and cleave full length teneurin-1 twice to liberate the cytoplasmic domain, in view that not any proteins are substrate of a specific protease, and that a substrate for an enzyme is usually specific for said enzyme.

2. Claims 1-9, 12-13, 31-33 are also rejected under 112, first paragraph, for lack of enablement of a complex of the cytoplasmic domain of teneurin-1 or **of a genus of cleaved teneurin product and a genus of cellular targets, or PML, and a method for detecting teneurin-1 signaling using said complex.**

The specification only discloses a complex of the cytoplasmic domain of teneurin-1 and ponsin in the nucleus, supra. The specification however does not have any data, or objective evidence that the cytoplasmic domain of teneurin-1 is complexed with proteins other than ponsin in the nucleus. The specification does not have any data or objective evidence that any cleaved fragment of teneurin-1 is associated with ponsin.

One cannot predict, other than ponsin, which other target proteins, including those in the nucleus, would complex with the N-terminal, cytoplasmic domain of teneurin-1, as claimed in claims 1-9, 12-13, 31-32, because not any protein is complexed with a certain specific domain of a protein. Further, one cannot predict which proteins would complex with any fragment of teneurin-1, as claimed in claim 31, because not any fragment of a protein would bind to another protein. In addition, one cannot predict that PML would bind to teneurin-1, as claimed in claim 33, because not any protein is complexed with a certain specific protein.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Minet et al, 1999, J Cell Science, 112: 2019-2032.

Claim 31. (original) A composition comprising a cleaved teneurin product and a cellular target of the cleaved teneurin product.

Minet et al teach that the C-terminal fragment of teneurin-1, containing the YD repeat, binds to heparin sulfate in cell extracts (abstract, p.2024, second column, last two paragraphs).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
April 17, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643